Remarks/Arguments

Claims 1-15 are pending in the application. Claims 1-9 and 15 have been withdrawn from consideration pursuant to a lack of unity objection. Claims 10-14 are under consideration.

Election / Restriction Requirement

Reconsideration and withdrawal of the lack of unity objection as to all claim groups is respectfully requested. As pointed out in the Response to Restriction Requirement, the special technical feature of the invention is an immunogenic determinant which comprises a complex of a stress protein and an antigen.

The Examiner identifies this immunogenic determinant as the special technical feature, but fails to recognize that it is the composition of the immunogenic determinant and *not* the fact that it results from induction by stress, such as heat, which serves to differentiate it over the prior art.

Specifically, as provided in the present invention, the heat shock protein (stress protein) is derived directly from the extracellular pathogen's *own* heat shock protein , i.e., the heat shock protein is endogenous. This is in contrast to the heat shock protein – peptide complexes of the prior art where the heat shock protein is derived from the *host* organism which the extracellular pathogen is infecting, while the peptide complexed thereto is derived from the extracellular pathogen.

The immunogenic determinant provided in the claims is therefore comprised of a complex of a stress protein *and* an antigen which are *both derived from an extracellular pathogen.* Such a feature is not taught in the prior art. Further, this feature is a required element of all of the Groups I, II and III.

Stress-induced production of heat shock proteins is not restricted to heat as being the only stress inducing stimulus. Accordingly, the claims are not limited to heat as the stress inducing stimuli. However, irrespective of what stress-inducing stimuli is applied, the resulting stress

protein/antigenic peptide fragment complex is endogenous in that *both elements* are derived from the extracellular pathogen.

Accordingly, the method steps of claim 1 *do not* constitute the special technical feature, rather it is the extraction and subsequent use of the endogenous stress induced complexes.

The immunogenic determinant of claim 15 (Group III) is a stress protein/antigenic peptide fragment complex produced in-situ from the pathogen. Again, both the stress protein and peptide are endogenous.

Reconsideration and withdrawal of the lack of unity objection as to all claim groups is respectfully requested.

Response to Section 112, 1st paragraph Rejection

Examiner alleges that the specification does not reasonably provide enablement for "a vaccine composition comprising an immunogenic determinant, wherein the immunogenic determinant comprises one or more complexes between a heat shock protein and an antigenic peptide fragment derived from the heat treatment of an extracellular pathogen" – i.e. where the complex may be derived from any prokaryotic, protozoan or fungal species.

With regard to the points on enablement, it is pointed out that assessment of enablement is not based on whether any experimentation is necessary to perform the scope of the invention as defined in the claims, but rather whether the level of that experimentation is undue. Importantly, the fact that experimentation may be complex does not make it undue.

In the present case, the person of ordinary skill in the art would be substantially qualified and experienced in the field, having at least a post-doctoral level of qualification.

Examiner acknowledges that the instant specification adequately describes and provides supporting experimental methods and results exemplifying vaccines comprising one or more complexes between a heat shock protein (HSP) and an antigenic peptide fragment derived from the heat treatment of bacteria.

Examiner submits that the specification is not enabled for vaccines/methods containing/using HSPs other than those derived from treatment of bacteria. Accordingly Examiner submits that one skilled in the art would not be able to make and use vaccines other than those comprising bacterial derived HSPs without undue experimentation.

Page 1, lines 26 to 28 of the description teach HSPs forming a family of highly conserved proteins which are widely distributed throughout the plant and animal kingdoms. The skilled man is therefore familiar with the fact that the structure and function of HSPs is highly conserved. This conservation means that HSPs have the same (or very similar) structure and also perform the same function irrespective of the type of cell in which they are expressed.

Examples 1, 3 and 4 teach the induction of HSPs in *Mycobaterium Bovis*, *Mycobacterium Tuberculosis* and *E. coli/Salmonella typhimurium*, respectively. Conditions for induction of HSPs are described, as are methods for extracting and purifying the resultant HSP/peptide complexes such that they can be used as the immunogenic determinant in a vaccine composition.

The conditions for inducing HSP production described in Examples 1, 3 and 4 would also be those which would be used to induce HSP induction in other bacteria as well as in fungi and protozoa. The highly conserved nature of HSPs means that the function of HSPs in protozoa and fungi would be known by the skilled man to be the same as for bacteria. Accordingly, the skilled man would expect the conditions described in Examples 1, 3 and 4 to also be suitable for inducing HSP production in fungi and protozoa.

The method of extraction and purification of HSP complexes as described in Examples 1, 3 and 4 would also be the extraction method employed to obtain stress protein/antigenic peptide fragment complexes from fungi and protozoa where HSP production had been induced.

Accordingly, Examples 1, 3 and 4 provide teachings which can be directly applied to fungi and protozoa in order to induce HSP production and extract the resulting HSP/peptide complexes (stress proteins/antigenic peptide fragment complexes).

Further, the skilled man, having considered the examples provided in the instant description would be aware that there are differences in the control mechanisms relating to the expression of the HSP genes in Mycobacteria and those of *E. coli* and *Mycobacterium tuberculosis*. Although the HSPs which are produced in *Mycobacterium tuberculosis* and *E. coli* (or *Salmonella typhimurium*) are highly conserved in structure and function, the mechanisms which control the expression of these proteins are differ between mycobacterium and *E. coli*. The difference in these control mechanisms would be known to and appreciated by the skilled man. The skilled man would therefore appreciate that the described methodology relating to the induction of HSPs would be applicable to cells where different cellular control mechanisms were employed to control the expression of HSP genes.

Accordingly, having considered the teachings of Examples 1 and 4 of the present description, the skilled man would identify that the methods of the examples provided in the description result in stress protein/antigenic peptide fragment complex production in two different extracellular pathogens which exhibit two *different* control mechanisms for expression of stress proteins. The Examples therefore show that the methods described therein can be used to obtain stress proteins/antigenic peptide fragment complexes in a wide variety of extracellular systems. Accordingly, the skilled man would fully expect to apply the teachings of the instant description to induce and obtain stress proteins/antigenic peptide fragment complexes in fungi and protozoa.

Reconsideration and withdrawal of the Section 112, 1st paragraph, rejection is respectfully requested.

Response to Section 112, 2nd paragraph Rejection

Claim 10 is rejected as allegedly indefinite for the use of the phrase "peptide fragment derived from". The rejection alleges that it is unclear how the claimed product has undergone any chemical modification as implied by the recitation "derived". The rejection alleges that one skilled in the art can not ascribe a discrete and identifiable definition to the phrase.

Without conceding the correctness of the rejection, and in an effort to expedite prosecution, the word "derived" in claim 10 has been replaced with "obtained". It is respectfully submitted that the change in wording overcomes the rejection.

The term "extra-cellular pathogen" is defined at page 7, line 11. This term includes extracellular bacteria, extra-cellular protozoa, extra-cellular parasites and fungi. The skilled man would be aware that some bacteria are intracellular and that some forms of protozoa are intracellular. The skilled man would, however, know to identify such intracellular pathogens as being outside the definition provided for an extra-cellular pathogen.

The rejection of claim 11 is overcome by explicitly incorporating the method of claim 1 into claim 11.

Claim 12 is rejected because is unclear how the complex could be aqueous. However, the word "aqueous" does not appear in claim 12, but rather claim 13. The base claim, claim 10, defines a composition. The composition of claim 10 is open-ended with respect to the included complex of a heat shock protein and an antigenic peptide fragment. In claim 13, the composition is aqueous, that it, water or an aqueous medium is present along with the complex. It is not the complex that is aqueous, but rather the medium.

Claim 14 is rejected as being vague and indefinite because it recites a "method for treating an animal" but does not recite what the animal is being treated for. This claim has been amended such that it now reads "a vaccine *directed to an extracellular pathogenic organism*". It is clear from the context of the claim as amended that the animal is being treated for infection by an extracellular pathogen.

Reconsideration and withdrawal of the Section 112, 2nd paragraph, rejections is respectfully requested.

Response to Section 102 Rejection

Laminet et al.

Claims 10, 11 and 13 have been rejected as allegedly anticipated by Laminet et al.

Examiner submits that the GroEL/ES complex disclosed in Laminet is identical to the claimed vaccine. Laminet relates solely to the function of HSPs as chaperones. The teachings of Laminet are limited to HSPs forming complexes in relation to the function of HSP as a chaperone. There is no disclosure of the HSP complexes being immunogenic, or that these complexes can be used in a vaccine.

Claim 10 has been amended in order to clarify that the HSP which forms the complex with the antigenic peptide fragment is a "stress induced heat shock protein".

The HSPs (GroEL/ES) produced in Laminet are constitutively produced and *are not produced in response to stress inducing stimuli*. Accordingly, the Laminet disclosure teaches the reader that, under normal conditions, the HSP will form a complex with a peptide in its capacity as a chaperone. However, the Laminet disclosure provides no teaching of the function of GroES following heat stimulus, and in particular, whether heat-induced GroES would still bind peptides.

Examiner submits that the HSP complex disclosed by Laminet is identical to one produced/isolated by the method of claim 11. As defined above, the stress protein described in claim 11 differs from the HSPs defined in Laminet, in that the stress proteins of claim 11 are specifically induced following stress. The HSPs of Laminet are not produced in response to stress inducing stimuli, but rather, are constitutively expressed in response to the normal cellular functions of the cell.

Ferrero et al.

Claims 10, 11, 13 and 14 have been rejected as allegedly anticipated by Ferrero et al.

Examiner submits that the features of claim 10 can be derived from the document of Ferrero. However, the teachings of this document relate to the use of *recombinant* HspA and HspB of H. pylori. The co-administration of HspA and UreB (a subunit of *H. pylori* urease) was shown to induce immunity (p6499, column 2).

There is, however, an important distinction in using a recombinant HSP. Namely, there will be no peptide conjugated to the HSP. Hence, the immunogen is the recombinant HSP itself, *not* a complex of the HSP and an antigenic peptide as required in the present invention.

Further, the HSPs of Ferrero are not produced in response to a stress stimulus such as heat. Accordingly, the induced immunity illustrated by Ferrero relates to that induced by HSPs *alone* and not to stress induced HSPs in complex with antigenic peptides.

Examiner submits that the HSP complex disclosed by Ferrero is identical to the one produced/isolated by the method of claim 11. As detailed above, it is submitted that as the teaching of Ferrero uses a recombinant form of HSP, this must necessarily exclude any antigen or peptide which may be complexed to the HSP. Accordingly, Ferrero induces a response by means of an immune reaction directed to the HSP *only* and not to a complex of a HSP with a

peptide (antigen). Further, the HSP is not stress-induced, hence the benefit conferred by the present invention of heat-induced HSPs forming complexes with antigens which are more immunogenic than those formed between non-induced HSPs and peptides will not be obtained.

Srivastava (US Patent No 5,961,979)

Claims 10-14 have been rejected as allegedly anticipated by Srivastava.

Srivastava teaches HSP / antigen complexes which are formed in mammalian cells. As discussed in detail in the above section under "Election/Restriction Requirement", the present invention uses HSP (stress protein) which is derived directly from the extra-cellular pathogen's *own* HSP, i.e., the HSPs are endogenous.

The Examiner directs the Applicant to Srivastava column 5, lines 55-57, which state that stress proteins (as opposed to complexes as suggested by the Examiner) can be found in all prokaryotes and eukaryotes. This is a fact which would be well known to the skilled man. What Srivastava does not teach however is the use of HSPs derived from extra-cellular pathogens (such as prokaryotic HSPs) for use as an immunogenic determinant in order to induce immunity against that extra-cellular pathogen.

Accordingly, the teachings of Srivastava can be differentiated from the instantly claimed invention as the stress proteins which are disclosed in Srivastava are stress proteins which are derived from the *mammalian* cells, as opposed to stress proteins derived from an extra-cellular pathogen as provided in the instant invention. The use of HSPs derived from the extra-cellular pathogen as a basis to form the immunogenic determinant of the invention is a concept which is not disclosed or contemplated in the teachings of Srivastava.

Further, the complexes of the HSP and antigenic molecule disclosed in Srivastava did not result from stress induction. Accordingly, the benefit conferred by the present invention of heat

induced HSPs forming complexes with antigens which are more immunogenic than those formed between non-induced HSPs and peptides will not be obtained.

Wallen et al. (US Patent No 5,747,332)

Claims 10, 11 and 13 have been rejected as allegedly anticipated by Wallen et al.

This document relates to methods for the purification of HSP complexes. Wallen does identify that HSP-peptide complexes appear to work as vaccines. However, Wallen is not primarily concerned with the function of HSP-peptide complexes, rather, it considers improved ways to purify HSPs together with their associated peptide.

Wallen recognizes at column 3, lines 20-25 that the HSP-peptide association must be maintained in order to develop vaccines or immunotherapeutic tools for tumors and for infectious diseases.

A further aspect of Wallen describes a method for synthesizing HSP complexes and purifying the complexes so produced (column 3, lines 28-30). This facilitates binding of peptides to HSPs by passing the peptides through an ADP column to which purified HSPs are first bound. This method is not relevant to the instantly claimed invention as the present invention relates to the formation of stress protein/peptide complexes in extra-cellular cells following the induction of stress protein production with a stress stimulus.

Wallen makes no mention of stress protein induction. Accordingly, the benefit conferred by the present invention of heat induced HSPs forming complexes with antigens which are more immunogenic than those formed between non-induced HSPs and peptides is not disclosed, suggested or considered.

The Examiner refers to column 4, lines 49-67 as teaching that HSPs from bacteria such as GroEL and GroES (and also DnaK) can be used as HSPs to which peptides can be bound using the

method of the invention. However, using the synthesis method of Wallen to bind a peptide to GroEL/GroES does not result in a stress protein/peptide complex which is equivalent to the present invention. Firstly, the HSPs used are not HSPs which are induced following stressing of the cell. The present invention shows that stress protein/peptide complexes which are formed following stressing of a cell are *more* immunogenic than HSP-peptide complexes produced in a non-stressed cell.

Secondly, Wallen does not teach stressing an extra-cellular pathogen in order to form stress protein/peptide complexes, which can be used as in immunogenic determinant in a vaccine to be administered to a human in order to provide a prophylactic effect against infection by that extra-cellular pathogen.

Wallen only makes mention of DnaJ and GroEL/GroES with regard to their use in the synthesis of HSP complexes (column 3 and claims 20 and 22). Accordingly, there is no teaching or suggestion that HSPs from bacteria (or any other extracellular pathogens) can be used to induce immunity against that bacteria (or extra-cellular pathogen).

Hamel et al. (WO 96/40928)

Claims 10-14 have been rejected as allegedly anticipated by Hamel et al. Hamel relates to the use of HSPs as immunogens, not HSPs in complex with peptides as provided by the present invention. Examiner submits that the heat shock proteins isolated by Hamel would inherently lead to the isolation of stress/antigenic peptide fragment complexes.

The heat shock proteins provided by Hamel et al are recombinant heat shock protein molecules and not HSP/peptide complexes as provided by the instant invention. The recombinant HSP cannot, by definition, have a peptide conjugated thereto as this cannot be encoded for along with the HSP.

However, it could be argued that the examples describing the Hamel et al invention would include HSPs which are complexed to antigenic peptides, and that those HSP/peptide complexes would contribute to the production of the immune response which results from the preparations of the Hamel invention (as HSP/peptide complexes would be inherent in the antigen preparations prepared from *S. pneumoniae*).

It can be ascertained that the immune response shown in the Hamel et al examples is attributed to HSPs alone, and not HSPs in complex with peptides. This submission is supported by the following reasoning.

Hamel et al Figure 1 shows that heat shock at 45 degrees centigrade can result in the induction of HSP production. The heat shocking procedure is described at page 35, line 18. The preparation of the antigen preparations used to immunize the mice is described at page 34, line 36 through page 35, line 15. This methodology teaches the heat-killing of bacteria by incubating the bacterial suspensions in a water bath pre-warmed at 56 C for 20 minutes. However, incubation of the bacteria at this temperature for this length of time will result in the peptides disassociating from the HSPs. This will result in the HSP/peptide complexes present in the bacteria falling apart resulting in HSPs and peptides.

Accordingly, subsequent immunization with *S. pneumoniae* antigens (as described by Hamel et al at page 35, lines 33-38) would not result in immunization with an immunogenic determinant derived from an extra-cellular pathogens which comprise a stress-protein and a peptide separately, and not in combination.

Hamel et al Figures 3 and 5 show that the antibody response which results following immunization is directed to HSP72. Thereafter, all subsequent examples use *recombinant* HSP72. The experiments run using recombinant HSP72 provide the same results (presence and magnitude of immune response) as those obtained with the cell lysate HSP. Accordingly, it can

be concluded that the response which is seen following immunization with *S. pneumoniae* results from HSPs alone, and not HSPs in complex with peptides.

Labigne et al. (WO 95/14093)

The HSPs disclosed in Labigne are recombinant HSPs (as per those discussed in the Ferrero et al. citation). Such recombinant HSPs are not complexed with peptides. The immunogen is therefore the (recombinant) HSP itself, *not* the complex of the HSP and the antigenic peptide as required in the present invention.

Further, the HSPs of Labigne are not produced in response to a stress stimulus, such as heat. Accordingly, the induced immunity illustrated by Labigne relates to that induced by HSPs *alone* and not to stress induced HSPs in complex with antigenic peptides.

Further, the complexes of the HSP and antigenic molecule disclosed in Labigne did not result from stress induction. Accordingly, the benefit conferred by the present invention of heat induced HSPs forming complexes with antigens which are more immunogenic than those formed between non-induced HSPs and peptides will not be obtained.

In conclusion, none of the asserted references anticipate the claims of the application. Reconsideration and withdrawal of the Section 102 rejection is respectfully submitted.

Conclusion

The claims of the application are believed in condition for allowance. An early action toward that end is earnest solicited.

Respectfully submitted

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